A6
Cont.

31. (New) The cilostazol preparation according to claim 8, wherein said surfactant is one or more selected from the group essentially consisting of polyoxyethylene sorbitan fatty acid ester, polyoxyethylene alkyl ether and alkyl sulfate salt.

REMARKS

In response to the above Office Action, claim 1 has been amended to recite that the fine powder of cilostazol has an average particle diameter of 10 μm or less as set forth in claim 3 and that the dispersing and/or solubilizing agent is a surfactant as set forth in claims 6 and 11. Claims 3, 6, and 11 have been cancelled as well as claims 2 and 5 in view of the amendments to claim 1. New claims 29-31 more specifically define the surfactant of claim 1. Support for these claims can be found on page 14, line 15 to page 15, line 6.

In addition, claim 20 has been amended to depend from all of the remaining cilostazol preparation claims and to include the sustained release coating material of claim 22 which has been cancelled. Finally, non-elected claims 15-19, 27, and 28 have been cancelled to advance the prosecution of the application.

As a result of the above amendments, claims 1, 4, 7-10, 12-14, 20, 21, 23-26, and 29-31 are now presented for further consideration.

Main claim 1 as amended relates to a cilostazol preparation of a fine powder of cilostazol having an average particle diameter of 10 μm or less in a surfactant as a dispersing and/or solubilizing agent. Preferred surfactants are set forth in claims 7, 13, 14, and 29-31, the most preferred being sodium lauryl sulfate. Applicants found that such a composition has significantly improved dissolvability, particularly in the lower digestive tract.

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Cilostazol is produced by a chemical synthesis resulting in a bulk cilostazol powder typically having an average particle diameter of 20 μm or so. This powder has a low absorbability in the lower digestive tract and its absorbability is not improved even with a dispersing and/or solubilizing agent. See page 4, lines 4-9 of the specification. Up to now cilostazol powder having an average particle diameter less than about 20 μm has not been known in the art and particularly not a powder having an average particle diameter of 10 μm or less.

In the Office Action, the Examiner rejected claims 1-14 for being anticipated by Patel et al. (U.S. Patent No. 6,294,192). Reconsideration of the rejection in light of the amendments to the claims and the following is requested.

Patel et al. relates to a pharmaceutical composition of a "hydrophobic therapeutic agent" and a carrier, the carrier being a combination of a hydrophobic and a hydrophilic surfactant. An example of an agent is cilostazol (column 22, line 43) and of a surfactant is sodium lauryl sulfate (column 18, line 53). While "cilostazol is mentioned as a suitable "hydrophobic therapeutic agent," it is noted that it is listed along with literally hundreds of other agents. See column 22, line 7 to column 24, line 58 of Patel et al. Moreover, cilostazol is not listed as one of the "preferred hydrophobic agents" (column 24, lines 59 - column 25, line 5) and all of the Examples relate only to progesterone and cyclosporin, none to cilostazol.

In any event, it does not appear that anything is mentioned about the particle size of any of the agents, not even the preferred agents cyclosporin and progesterone. The Examiner refers to column 28, line 41 to column 30, line 35 of Patel et al. where particle sizes of "less than 20 nm" are mentioned. It is presumed from this, that the Examiner believes that since the pharmaceutical compositions of Patel et al. have particle sizes

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"less than 20 nm," that the particle sizes of the hydrophobic therapeutic agent incorporated into the composition must also be of the same size since they are essentially water insoluble. Column 21, lines 52-57.

However, upon more detailed study, it is apparent, especially with reference to column 30, line 27 of Patel et al., that this teaching of particle size relates to the particle size of the "aqueous dispersions" of the combination of surfactants (i.e., the carrier) used to form the pharmaceutical compositions, not the particle size of the pharmaceutical compositions. This is clear form Examples 7-12 beginning in column 36, line 25 of Patel et al. relating to "Average Particle Size." Note that while particle sizes for "compositions of the present invention" were measured, that the measurement actually was "made for the dispersed carrier, in the absence of a hydrophobic therapeutic agent" (Emphasis added). From Table 24 in column 37, these "aqueous dispersions" had particle sizes ranging from " about 6 to about 15 nm" (column 37, lines 25-26). This is consistent with a characterization of "less than 20 nm." It is clear therefore that it is only the "aqueous dispersions" used to form the compositions that had particle sizes of "typically less than 20 nm." Compare column 36, lines 55 to 61 with column 30, lines 25-29 and the reference in both to "aqueous dispersions." See also column 28, lines 53-56 where it refers to "dispersions" of the pharmaceutical compositions that had this particle size, not the actual compositions including the agent.

Accordingly, it is submitted that it cannot be assumed, as the Examiner has apparently done, from the teaching in column 28, lines 53-56 or column 30, lines 25-27 of Patel et al. that the particle sizes of even the preferred agents (i.e., cyclosporin and progesterone) let alone cilostazol were of "less than 20 nm."

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Since Patel et al. fails to teach any particle sizes for any of the hydrophobic therapeutic agents including cilostazol, it is submitted that none of the claims can be considered anticipated by the reference because they all recite "a fine powder of cilostazol having an average particle diameter of 10 μm or less." Withdrawal of Patel et al. as a ground of rejection under 35 U.S.C. § 102 is requested. It is noted that the proper rejection is under 102(e) not 102(a) since Patel et al. issued after the March 21, 2000 effective filing date of this application.

The Examiner also rejected claims 20-26 for being obvious over WO 97/48382 in view of Patel et al. Claims 20-26 relate to a sustained release preparation of cilostazol containing any one of the cilostazol preparations of the product claims and a sustained release coating agent.

WO 97/48382 may teach the combination of cilostazol and a sustained release material, but as acknowledged by the Examiner, it like Patel et al fails to teach the claimed particle size. The Examiner again makes reference to the teaching of particle size in Patel et al., but as discussed above, this particle size relates to the aqueous dispersion of the surfactants used to form the pharmaceutical compositions of Patel et al., not the actual composition containing the therapeutic agent. Thus this is not a teaching of the actual particle size of the agent. This is taught in neither of WO 07/48382 or Patel et al.

As set forth in M.P.E.P. §2143, to establish a prima facie case of obviousness, the prior art references relied on must in combination teach or suggest all the claim limitations. Since neither WO 97/48382 nor Patel et al. teach the claim limitation of a powder of cilostazol having an "average particle size of 10 μm or less," it is submitted the Examiner has not established a prima facie case of obviousness. Withdrawal of the

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combination of WO 97/48382 and Patel et al. as a ground of rejection under 35 U.S.C. § 103 is therefore requested.

Nor should the claimed particle size of 10 μm or less for the cilostazol powder be considered an obvious modification of the acknowledged prior art particle size of about 20 μm because of the significant increases in dissolution rates obtained by the preparations of the present invention. In support of this, enclosed is a Declaration of Mr. T. Mukai detailing the results of experiments he conducted comparing the water dissolution rates of cilostazol preparations containing cilostazol powder having particles sizes of 10 μm or less (Experiments Nos. 1-4) with a preparation containing a powder having a particle size of 22.2 μm (Experiment 5). With reference to the results in Table 1, Mr. Mukai concludes that preparations containing cilostazol powder of 10 μm or less (i.e., 2.0 μm, 2.5 μm, 3.4 μm, and 5.4 μm) exhibit much higher dissolution rates than that containing cilostazol powder of about 20 μm (i.e., 22.2 μm).

It is believed claims 1, 4, 7-10, 12-14, 20, 21, 23-26, and 29-31 are in condition for allowance and such action is therefore requested.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.

Dated: April 28, 2003

By: _____
Arthur S. Garrett
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Application Number: 09/555,026
Filing Date: January 18, 2002
Attorney Docket Number: 6854-11

APPENDIX TO AMENDMENT OF APRIL 28, 2003

Version with Markings to Show Changes Made

Amendments to the Claims

1. (Amended) A cilostazol preparation having a capability of dissolving cilostazol even at the lower portion of the digestive tract, which comprises incorporating a fine powder of cilostazol having an average particle diameter of 10 μm or less as an active ingredient into a surfactant as a dispersing and/or solubilizing agent.

4. (Amended) The cilostazol preparation according to claim [3] 1, wherein said dispersing and/or solubilizing agent is incorporated within a range from 0.005 to 50 parts by weight based on 1 part by weight of cilostazol.

7. (Amended) The cilostazol preparation according to claim [6] 30, wherein said surfactant is an alkyl sulfate salt.

8. (Amended) The cilostazol preparation according to claim [5] 29, wherein said fine powder of cilostazol is a fine powder having average particle diameter of about 7 μm or less.

12. (Amended) The cilostazol preparation according to claim [11] 31, wherein said fine powder of cilostazol is a fine powder having average particle diameter of about 5 μm or less.

20. (Amended) A sustained release preparation of cilostazol which [contains] comprises any one of the cilostazol preparations [described in] of claims 1 [to 14] 4, 7-10, 12-14, and 29-31 coated with a sustained release coating material.

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21. (Amended) The sustained release preparation according to claim 20, which has a capability of [releasing] dissolving cilostazol even at the lower portion of the digestive tract.

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